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D 4.13
Adjuvant Therapy After Revascularisation

D 4.13.1
Introduction

Vascular and endovascular procedures suffer a risk of failure, either early, intermediate, or late. Several factors affect this risk, and the incidence differs considerably between various types of procedures. The main causes of failure can be categorised as (1) early—technical flaws or low flow or increased thrombogenicity; (2) intermediate (6–24 months)–intimal hyperplasia; and (3) late—progression of atheromatous disease.

Regarding open vascular procedures, factors that affect failure are the use of autogenous versus synthetic vascular conduits, endarterectomy versus bypass procedures, and the location of the procedure, for example, an aortic procedure compared with a distal reconstruction. This also relates to differences in the calibre of the recipient arteries, occlusive lesions in the inflow or outflow vessels, and the capacity of the collateral circulation.

Bypass patency also depends on the calibre and length of graft to be used. Progression of disease and risk factors such as smoking and blood lipids have a major implication on patency. At one extreme, an aortobifemoral graft with a perfect outflow carries at least a 90% 1-year patency, whereas the corresponding figure for a prosthetic femorodistal bypass with restricted run-off might be 30% or even less. Technical problems, encountered during surgery or caused by surgery, also greatly influence the immediate outcome of the procedure. The same kind of factors presumably influence the outcome of endovascular procedures. However, some of these procedures have only come into use recently, which means that less knowledge exists on the incidence and magnitude of the problems.

Current adjuvant pharmacological treatment aims to reduce either early failures due to thrombosis, intermediate graft occlusions due to intimal hyperplasia, or further progression of atherosclerosis. Even though vein grafts are at much less risk of developing occlusions than synthetic grafts, it is reasonable to discuss them together because most of the expected problems are of the same kind, though not of the same magnitude. Various pharmacological agents are in use to prevent thrombosis. The two most important categories are *antiplatelet therapy* and *anticoagulation*. Recently also, prostanoids and nitric oxide have been tried clinically. Although exerting antiplatelet effects, these compounds are discussed separately from antiplatelet therapy.

D 4.13.2
Antiplatelet Therapy

Acetylsalicylic acid

Acetylsalicylic acid (ASA) has been recommended on its own merits for reducing thrombotic events in all patients with PAD (see Recommendation 28, p S71). This discussion focuses on the use of ASA to assist the patency of revascularisation procedures. Acetylsalicylic acid has been investigated in randomised clinical trials, either alone or in combination with dipyridamole. In a 1982 report, patients with PTFE grafts for either above-knee or below-knee femoropopliteal bypass procedures were randomised to either placebo, ASA alone. or ASA plus dipyridamole, starting preoperatively.[1] For below-knee

grafts, no difference was found between the groups, whereas those patients on placebo undergoing an above-knee reconstruction had a significantly worse outcome than those receiving ASA or ASA plus dipyridamole. In combined series with autologous veins and PTFE grafts, no patency differences were seen with placebo versus ASA or ASA plus dipyridamole treatment given postoperatively in two series.[2,3]

In a large series, 549 patients, all with a femoropopliteal autologous vein bypass, were randomised to treatment with either ASA plus dipyridamole or placebo.[4] Patients were followed-up for 3 years, and there were no differences in patency rates recorded between the groups. Conversely, the Antiplatelet Trialists in their meta-analysis found that not only survival but also graft patency could be improved using ASA.[5]

A theoretical explanation for an early benefit of ASA is given in a study by Goldman et al,[6] finding a lower thrombogenicity index with ASA and dipyridamole treatment using ^{111}indium-labeled platelets. Based on current knowledge, ASA is recommended for those undergoing interventions. A Danish review recently concluded that there is evidence for lifelong treatment with ASA after infrainguinal vascular reconstructions.[7] The authors also recommended a rather high dose (300–500 mg ASA daily).

Recommendation 96: Antiplatelets as adjuvant pharmacotherapy after revascularisation
Antiplatelet therapy should be started preoperatively and continued as adjuvant pharmacotherapy after an endovascular or surgical procedure. Unless subsequently contraindicated, this should be continued indefinitely. Caution should be used in patients in whom use of anticoagulants is proposed.

Ticlopidine

Ticlopidine, as a more recent antiplatelet drug, has proved effective in preventing vascular complications.[8] A reduced platelet uptake on aortobifemoral grafts has been shown.[9] A recently published prospective, randomised, multicentre study has shown that ticlopidine compared with placebo after femoropopliteal or femorotibial saphenous vein bypass procedures in 143 patients increased both survival and 2-year patency of saphenous vein bypass grafts in the legs.[10] Some of the side effects of ticlopidine, such as thrombocytopenia,[11] do not appear to be present with newer ADP inhibitors such as clopidogrel.[12]

D 4.13.3
Anticoagulants

The use of unfractionated heparin (UFH) during vascular surgery is a widespread routine. Recently, it was shown that low-molecular-weight heparin (LMWH) is as effective an anticoagulant as UFH during infrainguinal bypass surgery.[13] Conversely, UFH has been used more selectively during the postoperative course. The main reason might be a risk of postoperative bleeding and a need for careful monitoring of coagulation parameters. The development of LMWH has changed this perspective considerably, and studies have pointed at beneficial effects of LMWH in the postoperative management of infrainguinal bypass.

A randomised controlled study comparing LMWH with ASA and dipyridamole[14] showed significantly better patency in the LMWH group, but restricted to patients with CLI. This study combined results achieved with both synthetic grafts and vein grafts. It has been suggested that the conclusions are less valid because only one fourth of the grafts were vein; the remaining were various synthetic materials, and all patients received LMWH for the first week postoperatively, after which the randomised scheme started. In another randomised controlled trial comparing LMWH and unfractionated heparin, it was shown that LMWH was superior and as safe as unfractionated heparin in prevention of early graft thrombosis.[15]

Oral coumarin seems to increase patient survival, but controversies exist as to whether graft patency could be influenced. In two studies from Austria, it has been shown that graft patency is improved in patients with saphenous vein grafts receiving oral anticoagulation. Both primary graft patency and limb salvage were significantly increased.[16,17] In the first of these two studies, this effect was restricted to patients operated on for CLI. In this study, 12% of patients randomised to coumarin were withdrawn for bleeding complications. Contrary to these findings, a Swedish study, including patients receiving either vein grafts or synthetic grafts, did not indicate any better outcome in patients receiving oral anticoagulation during a 3-year follow-up.[18] The place for coumarin as adjuvant therapy after revascularisation procedures remains to be determined (see Critical Issue 30, p S170).

D 4.13.4
Other Drugs

Dextran

Dextran is able to reduce platelet uptake on graft surfaces[19] and was shown to be beneficial during fol-

low-up of "difficult lower extremity revascularisations" utilising either veins or synthetic grafts.[20] The graft occlusion rate at 1 week was 20.5% in the control group and 6.9% (0% in vein grafts) in the dextran 40 group. By the end of the trial, the overall advantage of dextran 40 was statistically significant at all times up to and including 1 month and in the subgroup with umbilical vein or prosthetic grafts, significant benefit lasted up to 32 months. However, there was no advantage in vein graft bypasses unless they were carried to crural arteries.[20] The latter has been confirmed in a recent single-centre prospective randomised trial.[21]

Dextran has been used extensively in Sweden, but there are few published studies that compare dextran with other forms of treatment. Recently, dextran 70 was compared with LMWH for distal vascular reconstructions. New data indicate few differences, except considerably more side effects with dextran.[22] Although anaphylactic reactions have been mitigated by pretreatment with the hapten, other complications such as wound bleeding and vascular overload are not uncommon unless a strict protocol is followed and certain categorical exclusions observed such as recent myocardial infarction, congestive heart failure, and renal insufficiency, particularly in patients with diabetes. On this basis, dextran 70 cannot be recommended as a routine measure and should only be used in those distal bypasses in which there is a predictably high risk of early thrombosis (eg, non-autogenous reconstructions or crural bypasses) and no contraindications.

Prostanoids

Prostanoids such as the prostacyclin analog iloprost have antiplatelet effects but also have effects on white cell aggregation and adhesion as well as on vasoconstriction. Flow increases in vein grafts during distal vascular reconstructions after iloprost injection have been shown.[23] In a large European multicentre study on patients with CLI comparing iloprost and placebo in distal vascular reconstructions using either vein grafts or synthetic grafts, no significant improvement could be shown with respect to the 1-year patency.[24] Whether this failure could be attributed to the short time of drug administration, only during the day of surgery and 2 subsequent days, is uncertain but may be a possibility. Interestingly, synthetic grafts performed better during the first month, when patients were treated with iloprost.

Nitric oxide

In a small series, nitric oxide has been administered during infrainguinal bypass surgery, resulting in an augmented graft flow and inhibition of depleted plasma antioxidants. Results on patency have not yet been presented.[25]

D 4.13.5
New Approaches

Activation of the glycoprotein (GP)IIb/IIIa on the platelet surface is the final pathway of platelet aggregation, regardless of the initiating stimulus. Inhibitors of GPIIb/IIIa receptors include monoclonal antibodies and peptidic as well as nonpeptidic synthetic specific receptor blockers. Abciximab exchanges between and binds to platelets for as long as 2 weeks, whereas synthetic GPIIb/IIIa inhibitors block ex vivo platelet aggregation only a few hours after the end of an infusion but have the advantage of also being orally active. New ways to interfere with the complex coagulation system abound. Direct inhibitors of thrombin is one of the recent pharmacological approaches being evaluated in clinical trials. Other approaches are synthetic inhibitors of factors VIII, IX or X, tissue factor pathway inhibitors, or inactivated factor VIII.[26,27,28]

D 4.13.6
Adjuvant Therapy After Endovascular Procedures

For endovascular procedures, especially PTCA, anticoagulation has been advised, including oral anticoagulation. However, in recent studies, the need for oral anticoagulation has been questioned.[29] Vascular stents in the femoropopliteal region have been used without long-term anticoagulation, and reasonably acceptable early and intermediate patency rates have been obtained,[30] although other authors have routinely used coumarin.[30,31,32,33,34,35] In a Swedish multicentre study, patients were treated with ASA and dipyridamole or placebo after PTA of iliac and infrainguinal vessels. No differences were recorded between the groups with respect to the 1-year patency rate.[36]

D 4.13.7
Summary of Adjuvant Therapy

Even though randomised controlled studies are not entirely convincing, there seems to be consensus that adjuvant pharmacotherapy is needed to prevent graft thrombosis. Aspirin is the therapy most used, administered in a dose of 75 or 160 mg daily, although the low-dose/high-dose debate is not settled. In most of

the trials suggesting protected patency, the higher dose of aspirin was used.[1,2,3] Conversely, compliance may be a problem with the higher dose over time. Whether LMWH should replace aspirin, for example, for infrainguinal bypass, is not established. It seems important to start the treatment preoperatively. It seems reasonable to use the same policy for endovascular procedures as for surgical procedures, and a regimen with ASA is advised (see Recommendation 96, p S210).

D 4.13.8
Intimal Hyperplasia

Proliferation of smooth muscle cells causing hyperplastic growth, especially in the distal anastomosis of a synthetic graft or in the anastomoses or body of a vein graft, is the main cause of graft failure during a mid-term follow-up. Strict programs for graft surveillance give an opportunity to treat the lesion before any deleterious clinical effect, but most importantly, measures to prevent this hyperplastic growth have to be found. A major question is whether drugs that may reduce thrombogenicity are usable for this purpose as well. Drugs to be discussed are aspirin and heparin, UFH or LMWH. Clinical effects of aspirin and dipyridamole were seen after peripheral vascular surgery; however, with a short-term follow-up, this only proves an effect on thrombus formation.[37]

Heparin (UFH) has been shown to inhibit proliferation and migration of smooth muscle cells even in vivo.[38] In animal models, an effect on intimal hyperplasia has been evident, however, any clinical benefit in humans has not been proved.[39] It has been suggested that a continuous heparin infusion has to be used and also that LMWH has a greater effect on native arteries than on vein grafts.[40,41] Another proposal is that very high doses of heparin are needed.[42] The study reported above, intending to compare aspirin and LMWH, claimed a beneficial effect of LMWH on intimal hyperplasia.[14] This conclusion is not entirely evident, because the effect was seen mostly in patients with severe ischaemia, in which case an effect on thrombogenicity might be as important as an effect on intimal hyperplasia. Several experimental models have been tried to reduce intimal hyperplasia. Some of them are listed in Table 55. In addition, radiation and drug delivery from, or together with, implanted stents are under evaluation.[43,44]

Interestingly, almost all drugs reported in Table 55 exert a positive effect in the respective experimental model. Whether any of these findings will be possible to transfer to the human situation is too early to predict. Apparently, cholesterol reduction is an interesting possibility, because it promises to reduce atherosclerosis, but apparently also hyperplastic growth. Calcium channel antagonists, lipid-lowering drugs, and treatment of hypertension are all associated with reduced progression of atherosclerosis, especially if combined with smoking cessation and exercise. Whether this kind of treatment will also affect intimal hyperplastic growth has still to be proved. Both early thrombosis and late hyperplastic growth are multifactorial events, and it therefore would be most astonishing if one single drug could prevent them all. Concerning the cells involved, white cells, and to a lesser degree, platelets, are crucial. Maybe there is a future in drugs acting in different ways to reduce platelet activity. Synergistic effects have been shown with drugs acting on different pathways, and a combination of cGMP- and cAMP-elevating and cyclooxygenase-inhibiting drugs may be useful. Most certainly, there will also be techniques to inhibit the effects of activated white cells participating in the inflammatory response.

Critical Issue 38: Agents to inhibit intimal hyperplasia

There is a need to determine the clinical efficacy of agents reported to inhibit intimal hyperplasia in animal models. Because intimal hyperplasia is a major cause of failure of both percutaneous and open surgical revascularisation procedures, research aimed at its prevention is of critical importance.

Table 55: Compounds used in animal model experimental settings to reduce intimal hyperplasia

Compound	Experimental setting	Effect
Naroparcil[45]	arterial injury	+
Scavengers[46]	vein grafts	-
L-arginine[47,48]	vein grafts	+
Angiotensin-converting enzyme inhibition[49]	PTA	+
Cholesterol reduction[50]	vein grafts	+
Ketanserin[51]	vein grafts	+
FGF saporin[52]	PTFE grafts	+
VEGF[53]	vein grafts	+
Cyclosporin[54]	aortic transplant	+
Lazaroids[55]	vein grafts	+

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D 4.14
Surveillance After Revascularisation

D 4.14.1
Introduction

Despite a high likelihood of immediate success, all lower-extremity revascularisation procedures have a significant rate of failure over time (see also B 4.4, Surgery for Intermittent Claudication, p S97). It is now well recognised that patency of the treated arterial segment is most effectively preserved through surveillance programs that are capable of identifying flow-limiting lesions before complete occlusion of the conduit or vessel.[1,2,3,4] Revision of failing reversed saphenous vein bypass grafts, for example, results in excellent long-term graft function, with assisted primary patencies of 82% to 92% at 5 years.[5,6] Once complete occlusion has occurred, thrombectomy and revision yields a poorer secondary patency of only 43% to 76% at 5 years.[7,8,9] Similarly, the treatment of complete re-occlusions of angioplasty sites has a lower likelihood of technical success, a higher incidence of complications, and yields a less durable result.[10,11]

Clearly, the identification and treatment of flow-limiting lesions within the treated arterial segment before thrombosis of the segment provides a more durable result. Surveillance programs, therefore, represent a potentially valuable adjunct to every type of vascular intervention performed for the preservation of lower extremity perfusion. Because not all peripheral interventions are easily evaluated, the methods that provide the most cost-effective surveillance in a given setting remain controversial.

D 4.14.2
Methods of Surveillance

A number of methods of posttreatment surveillance of patients undergoing lower extremity revascularisation have been practised over the past several decades. These include clinical examination, ankle:brachial indices, duplex imaging, and arteriography. Additional study methods have been used, such as segmental pressures and plethysmography, but little information exists regarding the utility of these technologies.

Patient history and clinical examination

Most patients (66%) who have undergone femoropopliteal or femorotibial bypass procedures experience a return of preoperative symptoms imme-